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Original Article

Early child growth: how do nutrition and infection interact?

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Abstract

It is well known that the relationship between child nutrition and infection is bidirectional, i.e. frequent illness can impair nutritional status and poor nutrition can increase the risk of infection. What is less clear is whether infection reduces the effectiveness of nutrition interventions or, vice versa, whether malnutrition lessens the impact of infection control strategies. The objective of this paper is to review the evidence regarding this *interaction* between nutrition and infection with respect to child growth in low-income populations. Even when there are no obvious symptoms, physiological conditions associated with infections can impair growth by suppressing appetite, impairing absorption of nutrients, increasing nutrient losses and diverting nutrients away from growth. However, there is little direct evidence that nutrition interventions are less effective when infection is common; more research is needed on this question. On the other hand, evidence from four intervention trials suggests that the adverse effects of certain infections (e.g. diarrhoea) on growth can be reduced or eliminated by improving nutrition. Interventions that combine improved nutrition with prevention and control of infections are likely to be most effective for enhancing child growth and development.

Keywords: malnutrition, diarrhoea, environmental enteropathy, supplementary feeding, micronutrients, hygiene, stunting.

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Introduction

Infections are very common in the first two years of life. For example, children under 2 years experience an average of three to five episodes of diarrhoea per year in developing countries (Fig. 1). In some countries, the rate is six to eight episodes per year. Diarrhoeal incidence peaks at 6–11 months of age as infants eat increasing amounts of complementary foods that may be contaminated. At this time, they begin to crawl and explore their environment, putting them in direct contact with multiple sources of pathogens. During an infection, the immune system requires a broad range of nutrients to mount a defence against the invading organism. It has been hypothesized that nutrition interventions targeting growth may not be effective if infections are prevalent. On the other hand, improved nutrition may strengthen the child's ability to fight infection and reduce the negative effects of infection.

The objective of this paper is to review the available evidence on whether infection diminishes the positive impact of nutrition interventions on child growth and whether improved nutrition limits the

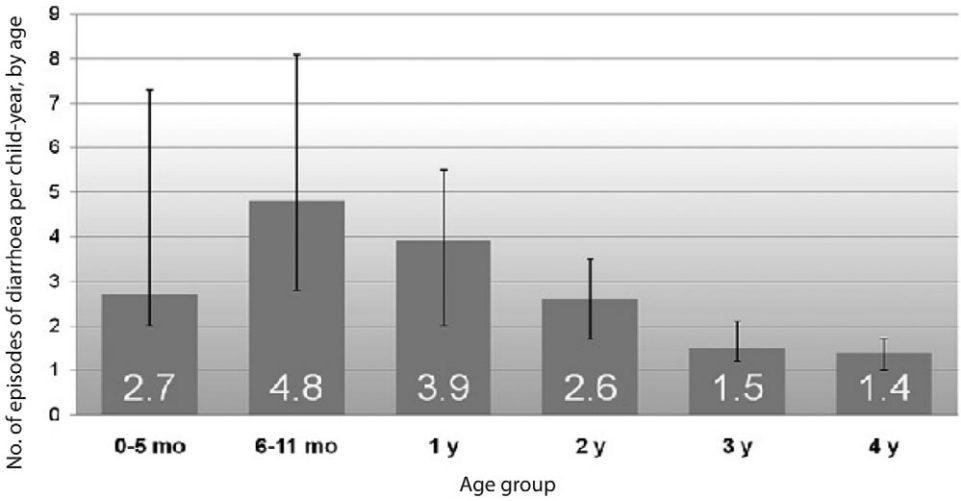

Fig. 1. Episodes of diarrhoea per year among children under five (Margaret *et al*. 2003). Bars represent the 25th–75th percentiles across 20 countries (1990–2000).

negative impact of infections on child growth – i.e. the *interaction* between nutrition and infection. Our purpose is not to examine the direct effect of nutrition on infection, which is a vast topic that goes beyond the scope of this paper. We begin with an overview of the relationship between child growth and the two most common categories of infection: diarrhoeal and respiratory infections. We then discuss the potentially growth-suppressing impact of subclinical infections and conditions, i.e. the ones that cause no obvious outward symptoms but may have important physiological effects. Next, we examine the evidence on whether there is an interaction between nutrition and infection with respect to child growth. We conclude with a brief discussion of the programmatic implications.

How strong is the impact of diarrhoeal and respiratory infections on child growth?

Diarrhoeal disease has many causes including pathogenic bacteria and other infectious microorganisms. In most cases, exposure to these pathogens occurs through the ingestion of contaminated food and water. Diarrhoeal illness is generally self-limiting,

Key messages

- Infections are very common in the first 2 years of a child's life.
- Even when there are no obvious symptoms, physiological conditions associated with infections can impair growth by:
  - Suppressing appetite
  - Impairing absorption of nutrients and increasing nutrient losses
  - Diverting nutrients away from growth
- There is little direct evidence that nutrition interventions are less effective when infection is common. Further research is needed.
- Four intervention trials showed that the negative effects of diarrhoea on growth can be reduced or eliminated by improved nutrition.
- Interventions that combine improved nutrition with prevention and control of infections are likely to be most effective for enhancing child growth and development.

meaning that the infection will run its course and the child will return to normal without requiring specific treatment. However, severe or persistent diarrhoea and repeated exposure to pathogens that affect the gut can have serious consequences. Diarrhoea robs the child of fluids and certain key nutrients such as zinc and copper (Castillo-Duran *et al*. 1988). If these fluids and nutrients are not replaced, the result can be severe dehydration, malnutrition, growth faltering or death in extreme cases.

It is normal for children to exhibit growth faltering during a bout of diarrhoea and to grow more rapidly than usual ('catch-up' growth) after recovery, but the extent of 'catch-up' growth may depend on the age of the child, the child's initial nutritional status, the specific pathogen(s) causing infection, the duration of the infection and the duration of the 'diarrhoea-free' interval following infection (Checkley *et al*. 1998; Wierzba *et al*. 2001). For example, children in Peru who were infected with the microorganism *Cryptosporidium parvum* experienced both weight and height growth faltering for several months post-infection followed by periods of 'catch-up' growth. Infants took longer to 'catch-up' in weight than children infected after 12 months of age, and those who were infected between birth and 5 months of age had a deficit of nearly 1 cm in height 1 year after infection, compared with non-infected infants (Checkley *et al*. 1998). Children who were already stunted (low length for age) at the time of infection did not catch up in either weight or height within 1 year after infection. Those who were not stunted at the time of infection achieved catch-up in weight within approximately 3 months and catch-up in height within approximately 6 months after infection, compared with their non-infected counterparts.

A high burden of diarrhoea in the first 2 years of life is associated with a much higher risk of stunting (height for age <–2 SD). In a pooled analysis of data from nine studies in five countries (Bangladesh, Brazil, Ghana, Guinea-Bissau and Peru), 25% of stunting at 24 months of age was attributed to having five or more episodes of diarrhoea in the first 2 years (Checkley *et al*. 2008). There was a 'dose–response' relationship between the cumulative burden of diarrhoea (e.g. proportion of days with diarrhoea) and the likelihood of being stunted at 24 months of age. Adjusting for socio-economic status did not alter these results.

The impact of respiratory infections on growth is less clear, in part because of a paucity of research on this relationship. The most common types of respiratory infections – mild, upper respiratory infections – are unlikely to have persistent effects in most children. But respiratory infections that include fever are linked with a higher risk of stunting. In a longitudinal study of children in the Philippines followed from birth to 24 months of age, the cumulative impact of febrile respiratory infections on risk of stunting was similar to that of diarrhoea (Adair & Guilkey 1997). Fever is one indicator of immune system activation, which (as explained below) can suppress appetite and lead to re-allocation of nutrients away from growth.

What is the role of subclinical infections and related conditions?

An infection is defined as subclinical when there are no obvious signs or symptoms, but there is physiological evidence of abnormality. Young children often test positive for certain infections (e.g. *Helicobacter pylori*, Epstein–Barr virus, cytomegalovirus, mycobacteria, cryptosporidium and even HIV) without exhibiting clinical symptoms. Many children also carry malaria parasites or gastrointestinal parasites with no outward signs. Subclinical abnormalities of the gastrointestinal tract, presumably caused by frequent exposure to pathogens, are also thought to be common. Even though symptoms are not evident, these subclinical conditions may have a strong, perhaps cumulative effect on metabolic function and growth. Microorganisms in the gut play a critical role in these functions (Preidis *et al*. 2010). The types and relative amounts of different gut bacteria can be affected by the diet (De Filippo *et al*. 2010).

Environmental enteropathy

One subclinical condition that is likely to be prevalent in developing countries is environmental enteropathy (EE), also known as tropical enteropathy. This condition often has no outward manifestation but can cause nutrient malabsorption by changing the structure and

function of the small intestine. It has been hypothesized that EE causes growth faltering and may decrease the efficacy of nutritional interventions (Goto *et al*. 2009; Humphrey 2009).

EE has been linked to living conditions with poor sanitation and hygiene practices, and is thought to be caused by chronic ingestion of pathogenic microorganisms. Gut exposure to high levels of harmful microorganisms results in a near-continuous state of immune system activation (see next section), which is harmful to the affected individual. Evidence that EE is related to sanitation and hygiene practices is provided by studies of Peace Corps volunteers and US soldiers stationed abroad who developed the condition during their assignments and regained normal intestinal function upon returning home. Research from the 1960s suggested that nearly all residents of the developing world at that time showed some signs of EE (Haghighi *et al*. 1997).

EE is characterized by various small intestinal abnormalities in seemingly healthy individuals. EE can be diagnosed by microscopic examination of an intestinal sample or by laboratory tests for intestinal permeability (sugar ratios present in the urine) or antibodies indicating that bacteria have been able to cross from the intestines into the body (endotoxin-core antibody). In healthy individuals, the surface of the small intestine is covered in millions of tiny, finger-shaped projections called villi. This architecture has evolved to maximize the surface area of the small intestine to facilitate nutrient absorption (Fig. 2). In a person affected by EE, changes occur in the structure of the small intestine including decreased villous height, sometimes referred to as 'flat architecture' (Fig. 3).

Not all people with EE will experience complete loss of villi; however, regardless of villous architecture, people with EE have increased intestinal inflammation and other structural changes that indicate an elevated immune response (Sullivan *et al*. 1991). EE is typically associated with a 'leaky gut' (increased permeability of the intestinal tract) and impaired ability to prevent pathogens from breaching the intestinal barrier.

The potential pathways by which fecal contamination leads to EE and subsequently to child undernutrition are illustrated in Fig. 4. Exposure to the causative agents of EE appears to occur very early in life (Haghighi *et al*. 1997). In a comparison of intestinal tissues from stillborn fetuses and young infants in developing countries, the fetal tissues exhibited normal finger-shaped villi, but the tissues from infants showed the flat architecture associated with EE within 3 months after birth. These changes may result in malabsorption of certain nutrients such as vitamin

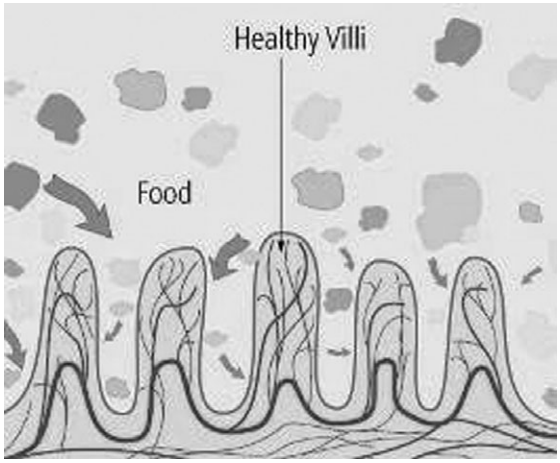

Fig. 2. Normal small intestine with healthy villi. http://duncanmarasanitation.blogspot.com/2009/09/tropical-enteropathy-3.html

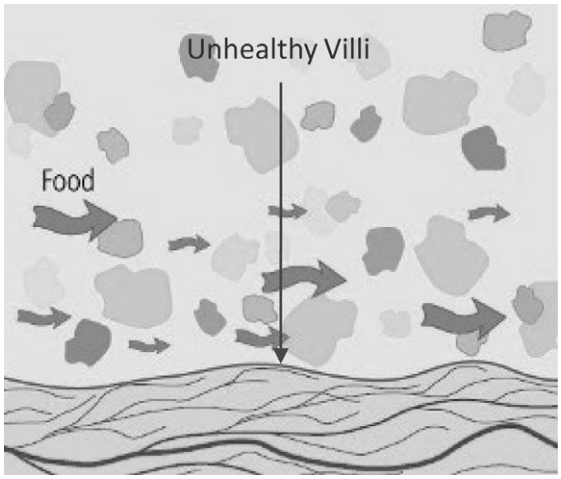

Fig. 3. Small intestine with environmental enteropathy characterized by unhealthy villi. http://duncanmarasanitation.blogspot.com/2009/09/tropical-enteropathy-3.html

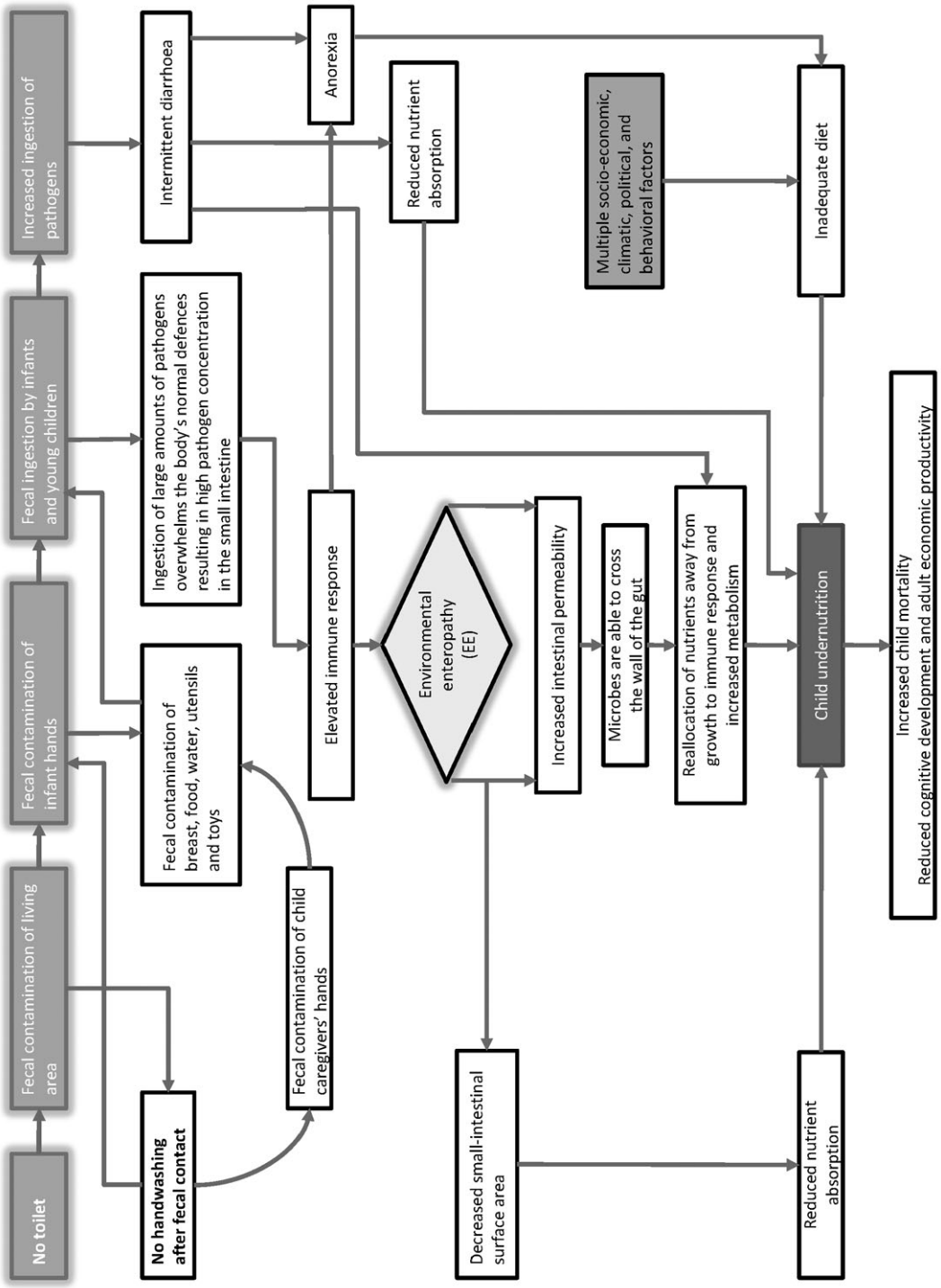

Fig. 4. Pathways by which fecal contamination leads to environmental enteropathy and child undernutrition (Adapted from Humphrey 2009).

B_{12} and fats (Haghighi *et al*. 1997; Ramakrishna *et al*. 2006; Humphrey 2009).

In a study in Peru, children in the worst conditions for sanitation and hygiene experienced 54% more diarrhoeal episodes between birth and 24 months of age and were 1 cm shorter at 24 months than children living in the best conditions. However, the association of water quality and sanitation with height was independent of the association with diarrhoeal disease. The investigators speculated that constant exposure to harmful bacteria could be causing EE and hindering the children's ability to effectively absorb and utilize ingested nutrients, regardless of whether it caused diarrhoea (Checkley *et al*. 2004).

EE is probably far more common than overt diarrhoeal illness in such settings. In a cohort of children in the Gambia, increased intestinal permeability was identified in 76% of the 922 samples collected from 119 children between birth and 2 years of age, whereas children were reported to have diarrhoea on 7.3% of all days during this period (Lunn *et al*. 1991). Based on the negative correlation between intestinal permeability and monthly length gain (corrected for age), the investigators calculated that impaired intestinal permeability accounted for 43% of linear growth faltering during this period. In a subsequent study (Campbell *et al*. 2003) in the same population, markers of intestinal function were normal at 2 months of age but deviated sharply from the norms by 15 months of age. The combined effects of three different markers of intestinal function were calculated to explain 56% of linear growth faltering. Because these were observational studies and the investigators did not control for potentially confounding variables, it is difficult to ascribe cause and effect, but the results point to the high prevalence of EE as a key risk factor for stunting in this population.

Immune activation, cytokines and appetite

In response to infection, the immune system becomes activated and produces specific immune cells and cytokines in large amounts to combat the invading organism. Cytokines are protein molecules that assist in fighting infection. They are beneficial in the short term; however, a chronic condition – like EE – can lead to continuously high levels of cytokines, which can cause negative metabolic consequences and suppress appetite (Wong & Pinkney 2004).

Reports of 'poor appetite' by caregivers of children under 2 in developing countries are common and may account for a substantial proportion of low energy intakes in this age group (Brown *et al*. 1995). Appetite is controlled by a group of chemicals called satiety hormones. Two important hormones involved in appetite regulation are ghrelin and leptin. Ghrelin stimulates food intake; leptin suppresses food intake. During infection, elevated levels of cytokines can lead to increased blood leptin concentrations and diminished appetite (Somech *et al*. 2007). This effect has been verified in cases of severe systemic infection such as neonatal blood infections (Orbak *et al*. 2003).

Immune system activation also lowers circulating levels of certain nutrients, in particular vitamin A and zinc, and increases iron retention in the liver, which restricts the availability of iron to other tissues in the body. These effects are probably part of an adaptive response to withhold key nutrients from invading pathogens, but they can result in inadequate availability of certain nutrients to support growth, even if intake is adequate, during the period of metabolic disturbance. Among children 6–20 months of age in Zambia, blood markers of inflammation (usually associated with infection) were negatively related to growth in length during the subsequent 3 months (Hautvast *et al*. 2000).

The 'dirty chicken' experiment

Studies of how sanitation affects the growth of newly hatched chickens provide clues that may be relevant to growth faltering of children in developing countries (Roura *et al*. 1992). A classic experiment conducted in 1992, called the 'dirty chicken' study, involved raising chicks in either steam-cleaned or unclean cages in close proximity with their own faeces. In each of the two living environments, the chicks were either administered an antibiotic cocktail or no antibiotics.

Unsurprisingly, living in close proximity to faeces in the poor sanitation environment caused the chicks raised without antibiotics to experience decreased

rates of weight gain, decreased efficiency of food utilization and increased levels of the cytokine plasma interleukin 1.

However, chicks raised in poor sanitary conditions and given antibiotics grew just as well and had the same low levels of circulating cytokines as chicks raised in steam-cleaned cages. The investigators concluded that the administration of antibiotics facilitated growth by preventing the immunologic stress and associated metabolic changes brought about by chronic exposure to faeces.

Researchers have attempted to treat EE in human children with antibiotics but with little success. In fact, in one study, provision of antibiotics led to an increased incidence of diarrhoea, perhaps due to a negative effect of antibiotics on the 'good' bacteria in the gut (Trehan *et al*. 2009). Short-term antibiotic therapy may fail because of re-exposure to fecal bacteria soon after treatment. Without improved sanitation and hygiene practices, a single course of antibiotics is unlikely to reverse EE, which may take months to resolve especially if there is repeated exposure to pathogens (Kirkpatrick *et al*. 2006; Thabane & Marshall 2009).

While prevention of infection-related growth faltering with antibiotics in humans may not be feasible, the 'dirty chicken' experiment indicates that living in poor sanitary conditions can cause growth faltering and implies that decreasing the burden of infection – including subclinical infection – may significantly improve growth outcomes.

What is the interaction between nutrition and infection?

Does infection make nutrition interventions less effective?

During infection, energy and other nutrients are diverted towards the immune response and away from growth. After all, survival is more important than continuing to grow, so growth faltering during infections may be an adaptive mechanism. However, repeated episodes of infection or persistent subclinical infection may put the child in a near-constant state of growth suppression. Does this mean that nutritional interventions for populations with high exposure to infections will be unsuccessful in improving child growth?

Evidence on this question is scant. In Indonesia, the effect of high-dose vitamin A supplements on linear growth in pre-school children (6–48 months of age) was dependent on the burden of respiratory infection (Hadi *et al*. 2003). In children with a low burden of respiratory infection, especially those with low vitamin A intake, linear growth improved after vitamin A supplementation. In children with a high burden of respiratory infection, there was little or no impact of vitamin A supplementation on growth regardless of vitamin A intake.

One potential explanation is that supplemental vitamin A is not well absorbed during an acute infection and a large proportion is excreted in the urine, rendering the high-dose supplement much less effective in improving vitamin A status if it is administered when the child is ill. Another potential explanation is that fever during respiratory infections causes metabolic changes that reduce circulating levels of vitamin A and make it less available to tissues to support growth. Regardless of the mechanism for the effect, the investigators concluded that coupling vitamin A supplementation programmes with efforts to reduce respiratory infections would increase the likelihood of a positive impact on growth.

Apart from the single study described above, there is little direct evidence that the impact of nutrition interventions is blunted when infections are common. Further research on this question is needed.

Does improved nutrition reduce the negative impact of infection?

The contrasting hypothesis is that improved nutrition can lessen or even eliminate the negative impact of infections on growth. The potential mechanisms by which improved nutrition could reduce the impact of infections on growth are shown in Box 1. These mechanisms include (1) strengthening the immune system; (2) compensating for malabsorption, reallocation or losses of key nutrients; (3) allowing for catch-up growth following infection; (4) enhancing appetite; and (5) favouring the growth of beneficial

Box 1. Improved nutrition may reduce the negative impact of infections on growth by

1. Strengthening the child's immune system, thereby reducing the severity and duration of infections and their impact on growth
2. Providing extra amounts of nutrients to compensate for those that are not well absorbed during infection, lost during diarrhoea, reallocated elsewhere in the body due to immune system activation or consumed in lower amounts than usual because of reduced appetite during infection
3. Providing the required amounts of nutrients for catch-up growth following infection, particularly the nutrients that are needed to build lean body tissue such as protein, potassium, magnesium, phosphorus, zinc and sodium
4. Preventing poor appetite caused by micronutrient deficiencies, thereby facilitating catch-up growth
5. Favouring the growth of beneficial bacteria in the gut that enhance gut function and immune defences

gut microorganisms. Four nutrition intervention trials among pre-school children in Colombia, Guatemala, Tanzania and South Africa indicate that provision of macronutrients and/or micronutrients can limit the negative effects of diarrhoea on child growth.

Randomized food supplementation study in Colombia, 1973–1980

Families were eligible for food supplementation if the mother was in the first or second trimester of pregnancy and at least half of her pre-school-aged children were underweight (Lutter *et al*. 1989). All household members in the intervention group received protein-enriched food that included powdered skim milk. Children in all groups were supplemented with iron and vitamin A. For the analysis of child stunting related to diarrhoea, the investigators used data for 241 children followed for the first 3 years of life for whom they had complete morbidity data and measurement of height (length) at 36 months of age (148 unsupplemented children and 140 children who were supplemented from the sixth month of pregnancy up to 36 months).

Diarrhoea was very common in the Colombia study. The number of episodes from birth to 36 months was 18 in the unsupplemented group and 16 in the supplemented group (not significantly different). In the unsupplemented children, height at 36 months was strongly inversely associated with the number of days ill with diarrhoea (–0.03 cm for each day of illness, $P < 0.001$). In the supplemented children, there was no relationship between diarrhoeal illness and height at 36 months (see Fig. 5, $P < 0.001$ for the interaction) (Lutter *et al*. 1992). The positive impact of supplementation on height (overall, approximately 3 cm) was greatest in children with the highest burden of diarrhoea (nearly 5 cm). The investigators concluded that nutritional supplementation eliminated the negative impact of diarrhoeal disease on child growth. They speculated that improved nutrient intake during and/or after illness episodes facilitated catch-up growth.

Supplementary feeding intervention in Guatemala, 1969–1977

A large supplementary feeding trial targeting pregnant and lactating women and their children from birth to 7 years of age was conducted in two sets of two matched villages. One village in each set was randomly selected to receive either a high-protein, high-energy supplement called 'Atole' or a non-protein low-energy supplement called 'Fresco', both fortified with several micronutrients (Martorell *et al*. 1995; Ramirez-Zea *et al*. 2010).

Among children 3–36 months of age who received Fresco, there was a significant negative relationship between the percentage of time with diarrhoea and length gain. By contrast, among children who received Atole, there was no significant relationship between diarrhoea prevalence and length gain ($P < 0.05$ for interaction effect) (Lutter *et al*. 1992). These findings were similar to those from the Colombia trial.

Vitamin A supplementation in Tanzania, 1993–1997

In this study, 687 children 6 to 60 months of age who had been admitted to the hospital with pneumonia were randomly assigned to high-dose capsules of vitamin A or placebo while hospitalized and, again, 4 and 8 months after discharge (Villamor *et al*. 2002).

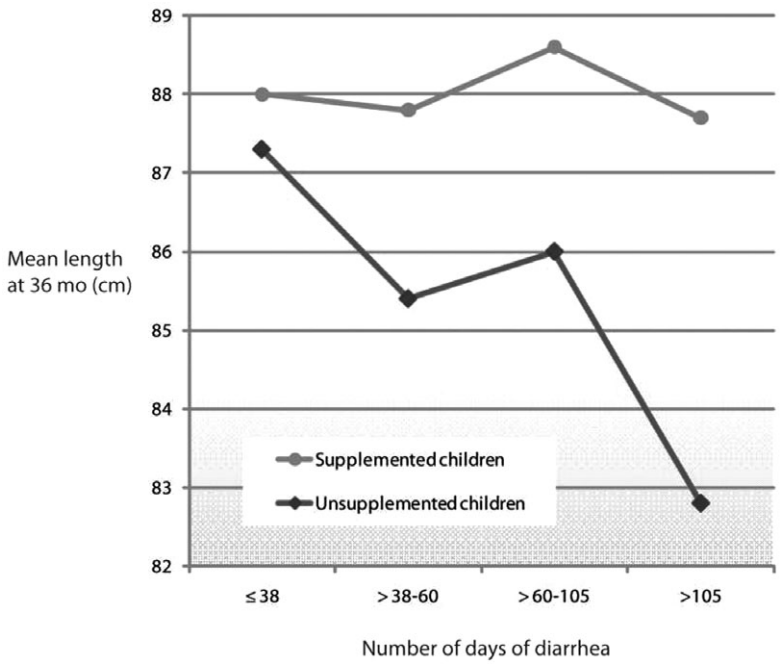

Fig. 5. Relationship between length at 36 months of age and number of days of diarrhoea during the first three years of life among supplemented and unsupplemented children in Colombia (Lutter *et al.* 1992).

There was no significant effect of vitamin A supplementation on growth for otherwise healthy children, but in children with persistent diarrhoea during the follow-up period, vitamin A eliminated the risk of stunting usually associated with this condition. Specifically, in the placebo group, the risk of stunting (adjusted for potential confounders) was 3.7 times higher in children with persistent diarrhoea than in those without persistent diarrhoea. In the vitamin A group, there was no risk of stunting associated with persistent diarrhoea ($P = 0.015$ for interaction effect). Children with persistent diarrhoea may have lower levels of circulating vitamin A than children with acute or no diarrhoea, so the vitamin A supplements may have compensated for this phenomenon and allowed for catch-up growth in children recovering from persistent diarrhoea. Although vitamin A is generally not considered a key growth-limiting nutrient (Golden 2009), ensuring adequate vitamin A may facilitate growth by restoring other physiological functions that must be normalized to permit rapid gain in lean tissue.

Micronutrient supplementation in South Africa, 2003–2006

In this study, 373 infants in three cohorts (32 HIV-infected children, 154 HIV-uninfected children born to HIV-infected mothers and 187 uninfected children born to uninfected mothers) were randomly assigned at 6 months of age to receive daily micronutrient supplementation for 18 months with either vitamin A, vitamin A plus zinc, or multiple micronutrients that included vitamin A and zinc (Chhagan *et al.* 2010). The study showed no overall impact on growth of zinc or multiple micronutrients compared with vitamin A alone (although there was a positive impact of multiple micronutrients on child length in those who were already stunted at enrolment). In the two cohorts of HIV-uninfected children, the addition of zinc or multiple micronutrients to vitamin A reduced the impact of repeated diarrhoea episodes on linear growth. This was most evident among children who had more than six episodes of diarrhoea per year ($n = 34$). In this subgroup, infants who received only vitamin A exhib-

ited a decline of 0.6 *z*-scores in length for age between 6 and 24 months of age, but those who received multiple micronutrients showed no decline in length for age during the same interval ($P = 0.06$ within this subgroup of 34). The investigators suggested that the progressive stunting usually observed in children with repeated episodes of diarrhoea may be related to deficiencies of certain micronutrients, and could be prevented by adequate intake of those micronutrients.

These four studies all show that the negative effects of diarrhoea on growth can be offset by nutrition interventions, at least in these particular situations. However, as mentioned above, clinical symptoms of diarrhoea may be just the 'tip of the iceberg' when it comes to gastrointestinal conditions that can affect growth. EE may be much more prevalent than diarrhoea. Whether nutrition interventions can reduce or eliminate the growth-suppressing impact of EE is unknown.

In adults, however, there is some evidence that multiple micronutrients may partially reverse the impact of EE on gut function. In a study of intestinal impairment in Zambia, 500 adults (with or without HIV infection) were randomly assigned to receive multiple micronutrients or placebo for 2 years. Micronutrients had no impact on markers of intestinal permeability, but there was a significant reduction in one of the markers reflecting bacterial movement across the intestinal wall (Kelly *et al*. 2010). This suggests an improvement in gut integrity or immune function, but further research, particularly in children, is needed.

To date, there is almost no information on whether improved nutrition can reduce the impact of infections other than gastrointestinal infections, such as respiratory illnesses, and malaria on child growth, although the Tanzania study described above showed that vitamin A supplements were more effective for improving growth in children infected with malaria or HIV than in non-infected children.

Some nutrients, such as iron, have the potential to increase the risk of infection, or mortality due to infection, and may interfere with linear growth (Dewey *et al*. 2002; Hurrell 2010). The mode of administration, such as supplementation vs. fortification, and the initial iron status of the individual are key factors to consider when evaluating whether nutrition interventions that include iron are likely to reduce or exacerbate the influence of infection on growth.

Conclusions and programmatic implications

Infections play a major role in preventing children in developing countries from reaching their growth potential. A high burden of diarrhoeal disease is a key risk factor for stunting, and other types of infections also contribute to growth faltering, although their impact is not as well documented. However, the view that 'disease rather than diet' is the main cause of growth impairment (Campbell *et al*. 2003) ignores the important interaction between infection and nutrition. To date, the limited evidence available suggests that nutrition interventions can substantially reduce or even eliminate the negative effect of diarrhoeal disease on child growth. This is encouraging, but it should be recognized that subclinical conditions such as EE may account for a large proportion of growth faltering, and it is not yet known whether improved nutrition can prevent or reverse the deleterious effects of EE (or growth faltering associated with infections other than diarrhoeal disease).

At present, evidence is insufficient to conclude that high rates of infection make nutrition interventions ineffective for improving child growth. Only one study was found that supported this hypothesis (Hadi *et al*. 2003). In this study, a high burden of respiratory infection limited the potential for vitamin A supplementation to improve growth. Clearly, further research on this issue is needed, but a single study involving a single micronutrient does not warrant holding back on efforts to improve nutrition in populations where infections are prevalent.

Nonetheless, combining improved nutrition with efforts to prevent and control infections will likely be the most effective approach for optimizing child growth and development (Box 2). This question was explored many years ago in the Narangwal Nutrition Experiment conducted between 1969 and 1973 in Punjab, India (Kielmann *et al*. 1983). In that project,

Box 2. Nutrition and infection prevention and control interventions to improve child growth

- Promote handwashing with soap and water
- Improve sanitation and water quality
- Promote exclusive breastfeeding for the first 6 months and continued breastfeeding thereafter
- Promote appropriate complementary feeding practices including feeding during and after illness and safe preparation and storage of complementary foods
- Step up efforts to prevent and treat respiratory illnesses and other infections such as malaria

10 villages were selected in clusters of two to three villages to receive a package of services that included either nutrition care (NUT), health care focused on infection control (HC), integrated services including both nutrition and health care (NUTHC) or standard care (control – symptomatic health care on demand only). NUT services included growth monitoring, food supplementation (initially only for malnourished children, but later made available to all children) and nutrition education. Health care services included curative and preventive care for common illnesses, immunizations and hygiene education. The target group was children under 3 years of age. At 36 months of age, children in the NUT or NUTHC villages were 1.3 cm taller than children in control villages, with no significant difference between NUT and NUTHC villages. Children in HC villages were taller than those in control villages, but not as tall as children in the NUT or NUTHC villages. Thus, in this setting, the combination of nutrition and health care did not produce a greater improvement in growth than nutrition care alone. However, the psychomotor development scores of children in the NUTHC villages generally exceeded the summed separate effects of NUT and HC, suggesting a synergistic effect on those outcomes. Apart from the Narangwal experiment, very little information exists on whether providing infection control together with direct nutrition interventions has an additive or synergistic effect on child growth or other key outcomes.

Key components of infection control are effective promotion of handwashing with soap and water and improvements in sanitation and water quality, which can significantly decrease diarrhoeal disease. In a recent meta-analysis (Cairncross *et al*. 2010), handwashing was linked to a 48% risk reduction of diarrhoea across study designs and pathogens. A substantial positive effect was also found for both water quality and sanitation improvements – 17% and 36% risk reductions, respectively. Access to and utilization of toilets is a high priority (Humphrey 2009), yet an estimated 2.6 billion people globally live without basic toilets to dispose of faeces (Coombes 2010).

An essential element of combined approaches is the promotion of breastfeeding for at least 2 years (exclusively for the first 6 months, and continued breastfeeding in combination with nutritious complementary foods thereafter), which has the dual benefit of reducing infection and improving nutrition. Other key practices, highlighted in the *Guiding Principles for Complementary Feeding of the Breastfed Child* (PAHO/WHO 2003), are feeding during and after illness to sustain adequate nutrient intake and promote catch-up growth, and safe preparation and storage of complementary foods to reduce foodborne illnesses.

Although many nutrition programmes already include hygiene messages, simply increasing knowledge and awareness about behaviours such as handwashing is not enough. Sustainable changes in behaviours are more difficult to achieve because of factors such as lack of access to clean water, long distance from water sources, the cost of hygiene products and poor design of educational interventions that do not take into account cultural beliefs or craft messages tailored to the needs and values of the target audience (Luby *et al*. 2008; Arnold *et al*. 2009; Aunger *et al*. 2009; Biran *et al*. 2009). The difficulty of improving household hygiene and sanitation practices, outside of intensive efficacy trials, is well recognized by researchers (Curtis 2003; Luby *et al*. 2008; Scott *et al*. 2008; Arnold *et al*. 2009; Luby *et al*. 2009). Innovative strategies have been suggested that focus on emotional motivations for behaviour change and engagement of professional consumer and market research agencies, rather than relying solely on knowledge-based approaches (Curtis 2003; Biran *et al*. 2009).

Research is needed on the efficacy and effectiveness of approaches that combine nutrition interven-

tions with multiple strategies for prevention and control of infections, including hygiene education, improvements in water quality and sanitation and measures to prevent and treat respiratory illness and other infections such as malaria. Development and evaluation of integrated cost-effective programmes designed to tackle these multiple objectives should be a high priority.

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Conflicts of interest

The authors have no conflict of interest to report.

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